Digestive Diseases and Sciences (2018) 63:2474–2479
https://doi.org/10.1007/s10620-018-4963-1

ORIGINAL ARTICLE

Procalcitonin as a Decision-Supporting Marker of Urgent Biliary Decompression in Acute Cholangitis

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Received: 4 November 2017 / Accepted: 2 February 2018 / Published online: 26 February 2018
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Abstract

Background and Aim This study aimed to evaluate the association of serum procalcitonin (PCT) at hospital presentation with disease severity and clinical deterioration to septic shock in acute cholangitis.

Methods This study included consecutive patients with a diagnosis of acute cholangitis who presented to the emergency department and underwent biliary drainage. PCT and blood culture tests were conducted at the time of initial presentation. Patients were categorized into three groups based on disease severity. White blood cell count, levels of C-reactive protein and PCT were compared regarding the following: cholangitis severity, blood culture positivity, and clinical deterioration to septic shock.

Results A total of 204 consecutive patients were enrolled, with grade I severity in 39 (19.1%), grade II in 139 (68.1%), and grade III in 26 (12.7%). The numbers of patients with blood culture positivity and clinical deterioration were 6 (15.4%) and 1 (2.6%) in grade I, 45 (32.4%) and 4 (2.9%) in grade II, and 14 (53.8%) and 1 (5.6%) in grade III cholangitis, respectively. Only PCT was significantly associated with blood culture positivity (3.25 vs 0.62 ng/mL; $P = 0.001$) and clinical deterioration (9.11 vs 0.89 ng/mL; $P = 0.040$). The cutoff value of PCT for clinical deterioration to septic shock among patients with grade I and II was 3.77 ng/mL (sensitivity of 80.0% and specificity of 74.0%).

Conclusion PCT could be a promising marker of clinical deterioration to septic shock in acute cholangitis. Therefore, PCT might be used as a decision-supporting biomarker for urgent biliary decompression.

Keywords Cholangitis · Drainage · Procalcitonin · Severity · Prediction

Introduction

Acute cholangitis is a serious inflammatory condition, usually caused by biliary obstructive lesions such as choledocholithiasis or pancreatobiliary tract malignancy. Timely biliary drainage plays a pivotal role in the management of acute cholangitis; antibiotics and fluid resuscitation are also important. Acute cholangitis has a wide range of severity, from a minor condition that improves with conservative medical treatment to severe disease leading to septic shock. However, acute cholangitis that is initially assessed as mild in severity could progress to severe sepsis and shock despite the use of empirical antibiotics, because disease severity does not imply responsiveness to medical treatment. Recently, serum procalcitonin (PCT) level at hospital presentation has been reported to be a useful predictor for clinical deterioration in critically ill patients [1]. Therefore, the aim of this study was to evaluate the association of serum PCT at hospital presentation with disease severity and clinical deterioration to septic shock in acute cholangitis, in order to determine the usefulness of PCT as an indicator for urgent biliary drainage.

Methods

Patients

This was conducted at a tertiary referral hospital between August 2015 and April 2016. Among all consecutive patients

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with a diagnosis of acute cholangitis who presented to the emergency (ER) department, patients who underwent biliary drainage were enrolled in this study. The decision to perform endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic biliary drainage (PTBD) was at the discretion of the treating physician. Exclusion criteria were: [1] previous history of treatment with ERCP or PTBD; [2] previous gastric surgery making endoscopic drainage impossible due to anatomical alteration; [3] serum procalcitonin not measured at initial presentation. The study was approved by the institutional review board with waiver of informed consent due to the retrospective design. The study followed the ethical guidelines of the 1975 Declaration of Helsinki. All authors had access to the study data, and reviewed and approved the final manuscript.

Management of Acute Cholangitis

All patients received parenteral antibiotics with a third-generation cephalosporin and metronidazole after blood culture and laboratory test. Volume replacement was conducted with crystalloid fluids. In cases of hypotension even after aggressive hydration, an inotropic agent was administered, in which situation the patients were regarded as being in septic shock. Parenteral antibiotics were continued until the inflammatory signs of acute cholangitis subsided. Response to initial medical treatment was evaluated by the treating physician, and then the timing and method of biliary decompression was determined at the discretion of the physician.

Methods and Statistics

The clinical history of each patient including time of presentation (day or night, weekday, or weekend), outcomes of the various diagnostic tests at initial presentation (white blood cell (WBC) count, C-reactive protein (CRP), PCT, bilirubin, albumin, prothrombin time, serum creatinine), the method of biliary decompression (ERCP or PTBD), and clinical outcomes were evaluated retrospectively. The severity of acute cholangitis at the time of initial presentation was assessed based on the Tokyo guideline 2013 (TG13). The clinical characteristics according to severity grade were compared using the ANOVA test with post-hoc analysis. Receiver operating characteristic (ROC) analysis was performed to determine the diagnostic sensitivity of each laboratory parameter for the severity grade. Independent t-test or Mann–Whitney U test was used for continuous variables, and Chi square test or Fisher's exact test was used for categorical variables. All P values are two-sided; $P < 0.05$ was considered statistically significant. Statistical analyses were carried out using IBM SPSS statistics version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical Features According to Severity Assessment

Baseline characteristics of the 204 patients are summarized in Table 1. The most common indication for biliary decompression was acute cholangitis caused by common bile duct (CBD) stone, and followed by malignant stricture. The number of cases of acute cholangitis according to severity grade was 39 (19.1%) grade I, 139 (68.1%) grade II, and 26 (12.7%) grade III. Among the three groups, the number of patients with positive blood culture results were significantly different ($P = 0.001$): 6 (15.4%) in grade I, 45 (32.4%) in grade II, and 14 (53.8%) in grade III, respectively (Fig. 1). The method of biliary decompression was also significantly different among the three groups. PTBD was preferred with increased disease severity ($P = 0.002$). The tendency for early biliary decompression was identified in patients with grade III severity, although this difference was not statistically significant ($P = 0.341$) (Table 2). Inflammatory markers, including WBC, CRP, and PCT, were significantly different according to severity grade (Table 3). However, ROC analysis for grade III cholangitis showed that WBC count could not significantly discriminate according to disease severity. The cutoff value of PCT for grade III severity was 1.76 ng/mL, with a sensitivity of 84.6% and specificity of 62.4% (Fig. 2A).

Relevant Laboratory Parameters for Blood Culture Positivity

The number of blood culture positive cases was 6 (15.4%), 45 (32.4%), and 14 (53.8%) in patients with grade I, II, and III severity, respectively. Although the number of blood culture positive cases was highest in the grade III group

Table 1 Baseline characteristics

	$N = 204$
Age, years—median (range)	76 (17–102)
Gender, female—no. (%)	86 (42.2)
Indication—no. (%)	
Common bile duct stone	182 (90.2)
Acute calculous cholangitis	137
Biliary pancreatitis	45
Malignant stricture	20 (9.8)
Cholangiocarcinoma	12
Pancreatic head cancer	2
Gallbladder cancer with bile duct invasion	3
Bile duct invasion from other malignancy	3
Benign stricture from chronic pancreatitis	2 (1.9)

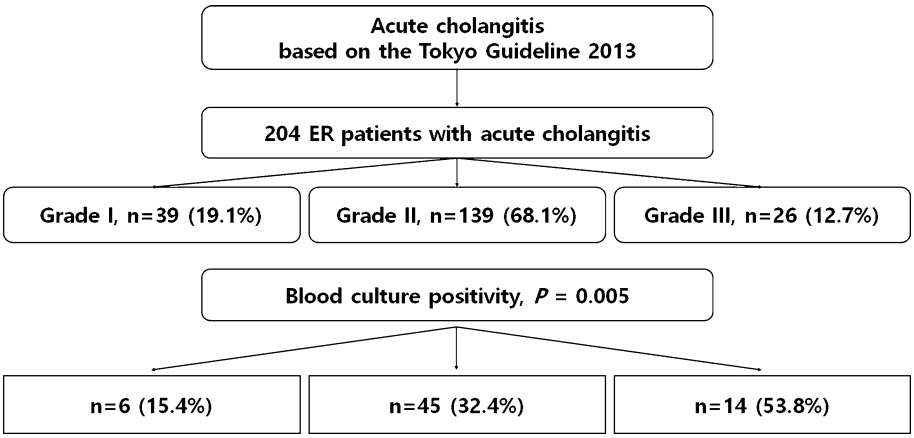


Fig. 1 Severity assessment according to the Tokyo guideline 2013 and blood culture positivity based on severity. One patient (2.6%) with grade I, 4 patients (2.9%) with grade II, and 1 patient (5.6%) with grade III severity progressed to septic shock before scheduled biliary decompression

Table 2 Hospital visit time and practice pattern according to the severity grade

Variables	Total ($n = 204$)	Grade I ($n = 39$)	Grade II ($n = 139$)	Grade III ($n = 26$)	P value
Hospital visit time – no. (%)					0.674
Daytime	126 (61.8)	26 (66.7)	83 (59.7)	17 (65.4)	
Off-hours	78 (38.2)	13 (33.3)	56 (40.3)	9 (34.6)	
Biliary drainage method – no. (%)					0.002
ERCP	140 (68.6)	35 (89.7)	92 (66.2)	13 (50.0)	
PTBD	64 (31.4)	4 (10.3)	47 (33.8)	13 (50.0)	
Timing of biliary drainage – no. (%)					0.341
Within 24 h	119 (58.3)	21 (53.8)	78 (56.1)	20 (76.9)	
From 24 to 48 h	38 (18.6)	8 (20.5)	28 (20.1)	2 (7.7)	
After 48 h	47 (23.0)	10 (25.6)	33 (23.7)	4 (15.4)	

Off-hours, weekend and nighttime during weekday; ERCP, endoscopic retrograde cholangiopancreatography; PTBD, percutaneous transhepatic biliary drainage

(14/26, 53.8%), it was also considerable in grade I and II groups (6/39, 15.4% in grade I; 45/139, 32.4% in grade II). Therefore, it is important to predict blood culture positivity, because it implies that the bacterial load is overwhelming and the patient carries a high risk of sepsis and septic shock. The CRP level and WBC count were not significantly different between groups based on blood culture result (culture positive group versus non-positive group). The level of PCT was significantly different between the two groups (3.25 vs 0.62 ng/mL; $P = 0.001$) (Table 3). The cutoff value of PCT for blood culture positivity was 0.68 ng/mL, with a sensitivity of 81.5% and specificity of 54.0% (Fig. 2B).

Serum Procalcitonin as a Promising Parameter for Clinical Deterioration to Septic Shock

Of the 204 patients, eight (3.9%) patients were diagnosed with septic shock at initial ER presentation. However, of the remaining normotensive patients, six (3.1%) progressed to septic shock before scheduled biliary decompression, including one patient (2.6%) with grade I, four patients (2.9%) with grade II, and one patient (5.6%) with grade III severity, respectively. When patients were classified into two groups based on progression to septic shock (progression group versus non-progression group), only PCT showed a significant difference between the two groups (9.11 vs 0.89 ng/mL; $P = 0.040$) (Table 3). The cutoff value of PCT for clinical deterioration to septic shock among patients with severity grade I and II was 3.77 ng/mL, with a sensitivity of 80.0% and specificity of 74.0% (Fig. 2c).

Technical and Clinical Success of Biliary Drainage

Among the 140 patients in whom ERCP was initially attempted for biliary drainage, deep cannulation of the bile duct was not successful in four patients, thereby leading to switch into PTBD immediately, while there were no cases of failed percutaneous biliary decompression among the 64 patients in whom initially PTBD was attempted. Therefore, technical success rates of ERCP and PTBD were 97.1 and 100%, respectively. Clinical signs of acute cholangitis were not completely resolved in two patients even after biliary

Table 3 Laboratory parameters according to the clinical features

	Cholangitis severity				Blood culture			Clinical deterioration to septic shock		
	Grade I ($n = 39$)	Grade II ($n = 139$)	Grade III ($n = 26$)	*P* value	Negative ($n = 139$)	Positive ($n = 65$)	*P* value	Progress to shock ($n = 6$)	Non-progress ($n = 190$)	*P* value
WBC count, $*10^3$ mm^3—median (IQR)	8.15 (7.42)	11.61 (7.23)	10.09 (13.57)	0.001	9.83 (7.04)	11.37 (6.58)	0.095	10.16 (5.87)	10.15 (7.11)	0.619
CRP—median (IQR)	0.77 (4.67)	5.26 (10.42)	12.68 (13.58)	0.001	4.26 (10.86)	5.51 (11.27)	0.331	5.57 (9.49)	4.22 (10.76)	0.875
PCT—median (IQR)	0.22 (0.52)	1.35 (4.67)	9.41 (53.69)	0.001	0.62 (3.78)	3.25 (8.86)	0.001	9.11 (18.52)	0.89 (4.34)	0.040

IQR, interquartile range; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin

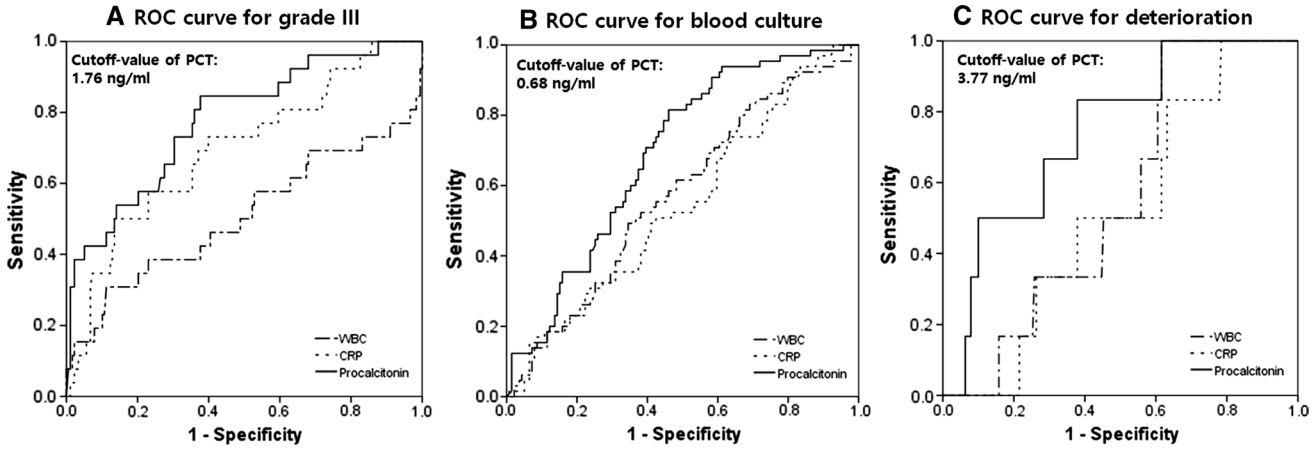
decompression using ERCP. Meanwhile, the clinical signs were improved in all of the patients in whom PTBD was initially performed, although additional procedures such as stone extraction or biliary stenting were needed subsequently when clinical parameters had become stable.

Discussion

Biliary tract drainage plays a crucial role in the management of acute cholangitis. According to TG13, the optimal timing of biliary drainage is different depending upon the severity of acute cholangitis: in grade I (mild) cholangitis, initial medical treatment including antibiotics may be sufficient; however, for non-responders, biliary drainage should be considered. In grade II (moderate), early biliary drainage is recommended, and in grade III (severe), urgent (as soon as possible) biliary drainage should be performed [2]. However, the time frame of biliary decompression in TG13 is somewhat ambiguous: "early" in grade II and "urgent" in grade III (severe). Moreover, even in grade I (mild) cholangitis, biliary drainage is recommended for non-responders to initial medical treatment. It is a critical point that even in mild cases at initial assessment, cholangitis can progress to include severe complications, such as sepsis and septic shock. Therefore, it is very challenging to decide whether to commence biliary decompression immediately or "watch-and-wait" with medical treatment, especially in patients presenting during the night or weekend, because the prediction of responsiveness to medical treatment is very difficult and accessibility to the drainage procedures might be low, especially during off-duty time.

In the present study, approximately 40% of the enrolled patients presented to the ER during off-duty time (weekend or night time during weekdays). The serum concentration of PCT at initial ER presentation strongly correlated with disease severity. Furthermore, it could well discriminate non-responders from patients responsive to initial medical treatment. The cutoff values of PCT for grade III severity and clinical deterioration were 1.76 ng/mL (sensitivity 84.6% and specificity 62.4%) and 3.77 ng/mL (sensitivity 80.0% and specificity 74.0%), respectively. Therefore, we suggest that PCT could be a promising decision-supporting biomarker that can help physician decide whether to commence immediate biliary decompression or not, especially in patients with borderline need for biliary decompression presenting at night time or the weekend.

CRP and WBC count are commonly used inflammatory markers for critically ill patients. However, these two markers are not specific for bacterial infection and can be elevated in non-infectious inflammatory conditions. Recently, PCT has gained increasing interest as a new biomarker for bacterial infection and sepsis [3–7], because the level of PCT has



	AUC	95% CI	P
WBC	0.506	0.360-0.651	0.926
CRP	0.695	0.582-0.808	0.001
PCT	0.778	0.680-0.876	<0.001

	AUC	95% CI	P
WBC	0.573	0.490-0.655	0.095
CRP	0.542	0.459-0.626	0.331
PCT	0.688	0.615-0.762	<0.001

	AUC	95% CI	P
WBC	0.560	0.408-0.712	0.619
CRP	0.519	0.344-0.694	0.875
PCT	0.746	0.581-0.912	0.040

Fig. 2 The receiver operating characteristic (ROC) curves and cutoff values of procalcitonin (PCT). **a** For grade III severity, the cutoff was 1.76 ng/mL (sensitivity 84.6%, specificity 62.4%). **b** The cutoff value for blood culture positivity was 0.68 ng/mL (sensitivity 81.5%, specificity 54.0%). **c** For prediction of clinical deterioration to septic shock, the cutoff value was 3.77 ng/mL (sensitivity 80.0%, specificity 74.0%). *ROC* receiver operating characteristic; *PCT* procalcitonin; *CRP* C-reactive protein; *WBC* white blood cell

been demonstrated to correlate with severity of infectious diseases [8–10]. Furthermore, PCT-guided antibiotic strategy is also reported to be effective for reducing the duration of antibiotic therapy, thereby decreasing the risk of antibiotic resistance and *Clostridium difficile* infection [11–13]. In healthy status, PCT is rarely released into blood stream because the PCT which is usually produced in the thyroid C cells is almost converted into calcitonin [14]. However, in a bacterial infection, especially sepsis, it could be produced in various tissues such as spleen, kidney, adipocytes, pancreas, colon and brain, thereby resulting in dramatic elevation of serum PCT levels [15].

Self et al. [1] demonstrated that serum PCT concentration at initial hospital presentation was associated with the future risk of respiratory failure or septic shock in community-acquired pneumonia and they suggested that admission to the intensive care unit should be considered in patients with elevated PCT level. From the perspective of risk prediction of clinical deterioration, this is in agreement with our results. Furthermore, Shinya *et al*. also reported that PCT could be a promising marker for the need of emergent biliary drainage in patients with acute cholangitis [16]. However, they did not evaluate the predictive role of PCT regarding disease progression to septic shock, but only demonstrated that a high PCT level correlated well with blood culture positivity and disease severity.

This study has certain limitations. First, this was a retrospective study, although the data was collected prospectively. The present study, however, had a relatively large number of homogenous patients who were managed at a single institution. Second, the serum PCT level was measured only once at initial admission, and thus changes in serum PCT level were not taken into consideration in this study; this could be another valuable factor to guide the implementation of biliary decompression. Recently, initial PCT value was reported to have significant value for predicting disease progression [1]. Therefore, the greatest utility of initial PCT measurement in acute cholangitis could be for those patients with borderline need for early biliary decompression, although PCT does not replace clinical judgement of the treating physician.

In conclusion, serum PCT concentration at initial hospital presentation has been shown to correlate well with acute cholangitis severity. In addition, it could be an early predictor of disease progression to septic shock in acute cholangitis. Therefore, PCT might be used as a decision-supporting biomarker for the urgent implementation of biliary decompression, especially in patients with moderate severity of acute cholangitis.

Author's contributions Yoon Suk Lee was involved in study concept and design, data acquisition and interpretation, and drafting of the manuscript; Ju Yup Lee and Yoo Jin Lee were involved in data acquisition; Kyung Sik Park and Kwang Bum Cho supervised the study and critically reviewed the manuscript

Funding This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP; Ministry of Science, ICT & Future Planning) (No.

2017R1C1B5018180) and by the Keimyung University Research Grant of 2016.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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